IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Frank B. Dean and A. Fawad Faruqi

Serial No.: 09/514,113 Art Unit: 1655

Filed: February 28, 2000 Examiner: B. Sisson

For: Method For Reducing Artifacts In Nucleic Acid Amplification

#7
1.pap

Assistant Commissioner for Patents
Washington, D.C. 20231

RESPONSE TO OFFICE ACTION

Sir:

Responsive to the Office Action mailed on October 25, 2000, please consider the following remarks. It is believed that no fee is required with this submission. However, should a fee be required, the Commissioner is hereby authorized to charge the fee to Deposit Account No. 01-2507.

Remarks

Claims 1-76 are pending. Claims 50-76 have been withdrawn from consideration as being drawn to a non-elected invention.

Applicants are claiming a method of reducing the formation of artifacts during nucleic acid amplification. In particular, applicants are claiming the use of template-deficient oligonucleotides as primers in the amplification reaction. Template-deficient oligonucleotides are defined in the specification on page 11, lines 7-11. A template-deficient oligonucleotide is an oligonucleotide with at least one region that cannot serve as a template for nucleic acid

synthesis. That is, there is a region of the oligonucleotide that cannot be replicated. Template-deficiency is not related to mismatched bases or unhybridized regions of a primer. In particular, template-deficient primers are not merely primers that have some mismatched bases with the target sequence. Such mismatched bases are not template-deficient because they are capable of serving as a template for nucleic acid synthesis. Template-deficient oligonucleotides are useful because they prevent full replication of any strand of nucleic acid into which they are incorporated.

Restriction Requirement

In the Office Action mailed October 25, 2000, the claims were divided into two groups, Group I, claims 1-49, drawn to a method of reducing formation of artifacts in a nucleic acid amplification reaction; and Group II, claims 50-59, drawn to template deficient oligonucleotides, and claims 60-76, drawn to related kits.

Applicants provisionally elected Group I, claims 1-49, for examination. Applicants now confirm this election.

Rejection Under 35 U.S.C. § 102

Claims 1-4, 7, 11-16, 19-25, 28-35, 37, and 42-49 were rejected under 35 U.S.C. § 102(b) as being anticipated by Sommer and Tautz, *Nucleic Acids Research* 17(16):6749 (1989). Applicants respectfully traverse this rejection.

The present claims require use of at least one template-deficient oligonucleotide as a primer in an amplification reaction. A template-deficient oligonucleotide is an oligonucleotide with at least one region that cannot serve as a *template* for nucleic acid synthesis (template-

deficient oligonucleotides are defined in the specification on page 11, lines 7-11). A primer with imperfect homology with a target sequence is not a template-deficient oligonucleotide. The mismatched bases can still serve as template when the primer sequence is replicated.

Sommer and Tautz disclose PCR primers that have extensive mismatches with the target sequence. Sommer and Tautz fail to disclose any oligonucleotide having any template-deficient nucleotides. Sommer and Tautz also fail to disclose any oligonucleotide that that would fail to be fully replicated. Thus, Sommer and Tautz fails to disclose at least one of the elements of the claims. Accordingly, Sommer and Tautz fail to anticipate claims 1-4, 7, 11-16, 19-25, 28-35, 37, and 42-49.

Rejection Under 35 U.S.C. § 103

Claims 1-49 were rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,656,461 to Demers, in view of Sommer and Tautz, Nucleic Acids Research 17(16):6749 (1989), and U.S. Patent No. 5,512,438 to Ecker. Applicants respectfully traverse this rejection.

The present claims require use of at least one template-deficient oligonucleotide as a primer in an amplification reaction.

Demers disclose the use of peptide nucleic acids to prevent reannealing of strands during PCR synthesis. None of the primers Demers uses are template-deficient. Demers fails to disclose or suggest any oligonucleotides having a combination of template-deficient and template-capable nucleotides. Demers also fails to disclose or suggest any template-deficient

primers. Demers also fails to disclose or suggest the use of only template-deficient oligonucleotides in an amplification reaction.

Ecker discloses oligonucleotides that bind to RNA secondary structure to prevent recognition of the RNA by its regulatory protein. Ecker discloses oligonucleotides for this purpose having modified nucleotides. Ecker fails to disclose or suggest any amplification method or use of the oligonucleotides in an amplification method.

Sommer and Tautz was described above.

None of the cited publications disclose or suggest what is claimed. Demers discloses only homogeneous peptide nucleic acids and does not use them as primers (indeed, such peptide nucleic acids cannot serve to prime nucleic acid synthesis; see column 3, lines 51-52). Demers does not disclose or suggest chimeric oligonucleotides having both template-deficient and template-capable nucleotides and provides no reason or rationale for using such oligonucleotides in an amplification reaction. Similarly, neither Ecker nor Sommer and Tautz disclose or suggest the use of such chimeric oligonucleotides in an amplification reaction and provide no reason or rationale for using such oligonucleotides in an amplification reaction. Thus, none of the cited publications disclose or suggest the use of oligonucleotides having both template-deficient and template-capable nucleotides in an amplification reaction.

Ecker, although disclosing oligonucleotides containing modified nucleotides, fails to disclose which modified nucleotides are template-deficient and fails to even hint that such a distinction has any significance. Neither Demers nor Sommer and Tautz disclose or suggest modified nucleotides that would be template-deficient. Thus, none of the cited publications

provide any suggestion to use template-deficient nucleotides, as claimed, rather than modified nucleotides in general. None of the cited publications suggest any of the advantages (or indeed any advantages) of using template-deficient nucleotides. Thus, there is no reason, based on the cited publications, for anyone to choose template-deficient nucleotides in oligonucleotides for use in an amplification, nor any suggestion to distinguish such template-deficient nucleotides from modified nucleotides in general. It was applicants who realized the advantages of using template-deficient nucleotides in oligonucleotides used in amplification reactions.

Thus, the cited publications, either alone or in combination, fail to disclose or suggest all of the features of the claimed method. Accordingly, the cited publications fail to make obvious the claimed method.

Allowance of claims 1-49 is respectfully solicited.

Respectfully submitted,

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No longer a firm per recipient 2/27/01

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